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Nutritional Aspects of Disease

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AN extensive review of much of the pertinent published data indicates that no reasonable doubt can be entertained regarding the important role performed by nutrition in the maintenance of a positive state of high grade health and in the prophylaxis and therapy of disease. The nutrients supplied to the tissues exert powerful direct influences not only as structural essentials for synthetic processes, but as regulators of all those biochemical processes that constitute the sum total of body metabolism. The ability of an animal to recover from an illness, injury or operation is closely related to its previous and current nutrient supply. Rare indeed is the animal that cannot be aided by proper nutritional guidance since nutrition is probably the most important environmental factor affecting health and disease.

There are ample critical, statiscally significant experimental studies to indicate that good nutrition is important for optimal resistance to infection, for a superior tissue capability to cope with disease and injury, and for maximum antibody production. Zucker (15) contends that present evidence indicates that certain B vitamins, notably pyridoxine, pantothenic acid and folacin play a significant role in antibody synthesis and that antibody production is diminished in severe deficiencies. Corynebacterium isolated from lesions of young pantothenic acid deficient rats produced a similar disease when inoculated into other pantothenic acid deficient rats, but rats on complete diets were resistant. The susceptibility to infection increased steadily from the tenth to fourtieth day on the pantothenic acid deficient diet. When non-inoculated rats were placed in contiguous cages, infection was widespread in those on a pantothenic acid deficient diet, while no infection developed in comparable animals on a complete diet or on diets deficient in pyridoxine or partially deficient in thiamine. However, some variation of rate of infection parallels certain different strains of rats.

Good nutrition will help to insure rapid wound healing after surgery, burns or radiation exposure. Normal blood protein levels, osmotic pressure and normal hematopoesis will be maintained by proper feeding. The principle factor in impaired wound healing according to Cuthbertson (16) is a cellular privation due to a lack of essential nutrients and the inaccessibilty of metabolites to the wound tissues. Protein starvation, due to lesions of various diseases in the oral cavities, is characterized by retardation of all phases of wound repair, but healing ultimately is accomplished. The benefits which result when methionine or cystine are supplied indicates the importance of amino acid sulfurs in wound healing. The simultaneous administration of any cortisone type of hormone results in depressed cell respiration and division and a decrease in circulating amino acids. An overdose of these cortisones induces cellular starvation.

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In general an attempt is made to supply all necessary nutrients through the ration. In major diseases, marked metabolic alterations may be produced by physiological stresses; losses of nutrients from the body may be unduly large and intake may be poor. Aitken (17) reported that disease processes, in most instances, greatly increase the nutritive requirements of all animals. The deficiencies resulting might be referred to as secondary, and are brought about by factors that interfere with ingestion, absorption or utilization of essential nutrients, or by factors that increase the requirements, or the destruction or excretion of these nutrients. The importance of nutritional deficiences that may exist as a result of a primary infectious process is not generally appreciated. Misleading advice is often given after nutritional deficiencies are observed in animals and it is concluded that the original disturbance was due to a dietary deficiency. The treatment and prevention of secondary deficiencies often are the decisive factors in recoverey after surgical operations and from many severe infectious diseases. Likewise, correction of secondary nutritional deficiencies often decide the success of other measures of treatment and restores animals to economical production in a shorter period of time. Probably the most important disturbances encountered that effect the nutritive requirements of farm animals are the diarrheal diseases. Fradkin (15) has pointed out that "diarrhea is probably responsible for more nutritional deficiencies than any other symptoms or group of symptoms" ...and that..."inadequate diets cause more therapeutic failures in the management of diarrheal disorders than any unwise choice of drugs or combination of drugs"...Diarrheal diseases are especially common in young calves. In most instances after this condition has existed for some time, calves give a remarkable response to various nutrients. However, in many instances the nutritional deficiency was the result of an infectious agent and not the result of feeding a poor ration. When feeding recommendations are made to prevent or correct secondary nutritional deficiencies their secondary nature must be clearly understood lest we forget their importance and begin to conclude that a faulty ration was the cause of the disturbance. The systematic course of diet prescribed in any instance will depend largely on the nature of the primary infectious process; i.e. protein and iron supplement in hemolytic diseases; electrolytes, fluids, protein hydrolysates and B vitamins in the diarrheal group of diseases. In general, consideration is given to initiating or maintaining the appetite, improving the quantity (and possibly the quality) of protein and supplying additional essential minerals and vitamins.

Carbohydrates in Nutrition and Disease

When it is considered that the amount of glucose circulating in the blood could supply only enough calories for ten to fifteen minutes of normal energy expenditures in the carnivorous farm animal, and that fifty times that amount of carbohydrate may be consumed at one time as exists in the circulating blood, it is evident that special mechanisms must operate to control absorption, storage and distribution of carbohydrate. Intestinal secretions contain the enzymes necessary to hydrolyse the starch, glycogen, dextrin, sucrose, maltose and lactose which normally constitute the carbohydrates utilized by nonruminants. Cellulose cannot be utilized, although complex carbohydrates of foods often classified as "crude fiber" may be partially available. (18) A controlled and limiting rate of intestinal absorption of the common sugars occurs, apparently as a result of the need for phosphorylation prior to absorption. A faster rate of fructose absorption possibly explains the more rapid effect of sucrose in alleviating hypoglycemia than the physiologic glucose. (19) It has been suggested that fructose is absorbed by simple diffusion and glucose by phosphorylation.

Thus, in "sprue" (a diarrhea, stomatitis, loss of weight, with frothy, fetid stools due to faulty fat and carbohydrate absorption) the glucose tolerance curve was found to be flat and abnormal, while the fructose tolerance curve was normal. (20) More recent studies on the absorption of sugars indicate a function of "adaptive

enzymes" in carbohydrate absorption. (21) After a period of fasting, sugars were absorbed less readily from the intestinal tract, and the feeding of glucose, fructose or galactose stimulated the absorption of the particular sugar administered for therapy.

Absorbed sugars are in part rapidly stored in the liver and muscles in the form of glycogen, and this process, as well as the reverse formation of glucose from glycogen, is controlled by the action of several hormones. It is not surprising, therefore, that liver conditions and endocrine disturbances, which are influenced greatly by the nutritional status of the individual, markedly affect carbohydrate metabolism. The findings of W. H. Price, D. F. Cori, and S. P. Colowice (22) that hexokinase (an enzyme which catalyzes the transfer of phosphate from adenosine triphosphate to hexoses, thus forming hexose-6-phosphate and adenosine diphosphate) is inhibited by anterior pituitary extract and that insulin relieves this inhibition is difficult to accept as the specific chemical basis for diabetes. There has been renewed interest in the value of fructose for parenteral injection in place of glucose, particularly in the diabetic canine. The fructose tolerance curve is apparently the same in the diabetic as in the normal individual, and this may be interpreted as indicating that the phosphorylating enzyme for glucose is under insulin control while that for fructose is not. In the growing diabetic rat (22) the urine volume, water intake and urinary carbohydrate were decreased when fructose was substituted for glucose in the diet, although the rate of growth was not affected.

The time required for deficiencies of riboflavin, pantothenic acid, and pyridoxine to develop have been shown to be dependent upon whether the diet contained glucose, dextrin or other carbohydrates. (23) It is assumed that such effects are generally due to variations in the intestinal flora which influence the intestinal synthesis of various vitamins.

The sudden introduction of a large excess of carbohydrate feed concentrates into the rumen for bacterial fermentation can cause among other things: dehydration, damage to the reticuloruminal epithelium, alteration of the bacterial flora, and the production of toxic amines. (25) Dehydration of the tissues undoubtedly occurs in the ruminant as a result of the increased osmotic pressure of the rumen contents following the sudden introduction of starch and/or sugar. The rumen is freely permeable to water which passes readily from the rumen to the blood, or vice versa, in conformity with the usual osmotic gradients (26). The rapid conversion of an excess amount of starch in the rumen into lactic acid and lactate increases the osmotic pressure of the rumen fluid. The introduction of sugar rich feeds (beets, apples, etc.) would likewise increase osmotic concentration of the ingesta with the diffusion of water from the blood into the rumen even if no fermentation occurred. The ruminal epithelium is a metabolically active tissue which is more directly exposed to the normal or abnormal fermentative processes of the ingesta than any other tissue of the body. Acute ruminitis, as the result of excessive carbohydrates, is characterized by large areas of necrosis in the wall of the rumen (91% of the lesions were in the anterior ventral sac of the rumen). The lesions become infected with *Spherophorous necrophorous* and eventually find their way into the hepatic portal circulatory system resulting in abscesses forming in the liver. In beef cattle slaughtered in the United States 37.6 per cent of the livers condemned can be traced to a ruminitis in the animal.

The excessive production of acids following the sudden introduction of large amounts of carbohydrate in the rumen causes a reduction in pH which kills susceptible bacteria, suppresses others and permits the growth of different varieties of bacteria. Therapy calls for the administration of normal rumen flora after the pH has been restored to its natural range (6.3-7.0). The production of toxic amines occasionally may be associated with the excessive ingestion of carbohydrates because a few plants contain proteins encased in the cellulosic membrane of the plant tissue cell. Histamine and tyramine

(Cont. on page 50)

(Cont. from page 17)
have been isolated from the ruminal ingesta of animals fed large quantities of wheat and corn. (27)

Proteins in Nutrition and Disease

Problems of tissue repair have received attention due especially to the fact that injury, whether physical trauma, burns, infection, or major surgical procedures, is associated with nitrogen losses, which may be very large. This so called catabolic phase occurs in normal individuals subjected to these stimuli, but is not usually seen in children or in undernourished adults. Unlike the reaction in starvation, this protein catabolic process usually cannot be interpreted by increasing the intake of highest quality protein and calories. In burns, nitrogen is lost in the exudate which forms, in addition to that lost by increased excretion due to catabolism. In the event of a burn corresponding to half the body surface of a man of average size, the increased urinary nitrogen loss may be great enough to correspond to two liters of plasma, to say nothing of the loss from the burned skin. (18) In other types of exudates associated with inflammatory processes, as much as fifty grams of protein may be lost per day. Protein deficiency may then lead to edema, delayed wound healing, impaired gastrointestinal function and the development of liver damage. Because of these considerations many advocate oral and parenteral protein feeding with sufficient or excess calories for patients subjected to trauma or burns. (28)

It is still too early to determine whether dietary factors, including the protein or amino acid composition of the diet, which animal studies indicate play a role in carcinogenisis, may also have a relationship to cancer as it appears in man. Diet has an important effect upon carcinoma in the experimental animal. For example, simple under nutrition or starvation will reduce the rate of growth of many tumors; however, the host suffers as well. The extraordinarily high incidence of liver cancer in the African Bantu and the extremely poor diet consumed by these natives have suggested a casual relationship, especially in view of the fact that cirrhosis of the liver has been found in almost every Bantu with hepatic cancer. (30)

In the absence of ascorbic acid in man, that is in clinical scurvy, tyrosine is improperly metabolized and large quantities of parahydroxyphenylpyruvate and related compounds are excreted in the urine. The situation is completely changed when the scurvy is cured by the administration of ascorbic acid. There was quite a flurry of interest in the use of glutamic acid to increase intelligence, following its supposed effectiveness in epilepsy. It is questionable, however, that glutamic acid has an important function in this regard. (29)

The sudden ingestion of large amounts of casein can be fatal to sheep. When sheep accustomed to fifty grams of casein daily with grass hay were fed one-hundred grams of casein, feed consumption and cellulose digestion were markedly reduced. Following the death of one animal, a marked odor of free ammonia was present in the rumen contents. (31)

Urea nitrogen can be substituted for about one-third of the natural proteins in a ration for cattle provided other nutrients necessary to balance the ration are supplied. The incorporation of larger amounts of urea in the ration have resulted in slower gains and general unthriftiness. A dosage of urea in excess of twenty grams per hundred pounds of body weight will produce urea toxicity in cattle. (32) The factors which predispose to urea toxicity from urea-containing feeds are starvation, low quality of roughage, rapid consumption by aggressive animals, sudden addition of urea to the ration, excessive quantity of urea in the ration and feeding urea without sufficient natural protein. For safety, the upper limits of urea in feeds for beef cattle should be: (a) 1 per cent of the total dry ration, (b) 2 per cent of the total grain ration, or (c) not more than 5 per cent of the mixed protein supplement. Actually, the toxicity of urea depends in a large measure upon the previous ration of the ruminant. If the previous ration was poor, the bacterial population is low and little ammonia is

utilized, so the excess may be converted to ammonium carbamate which is readily absorbed to exert its toxic effects. Increasing the ruminal bacterial population by the feeding better grades of hay and carbohydrates increase s the ability of the rumen to utilize the urea and thereby decreases the opportunity of toxicity from urea derivatives. (25)

Fats in Nutrition and Diseases

A rigorous exclusion of fat from the diet is required to produce the symptoms of "essential fatty acid" deficiency. Young rats maintained on a fat free diet do not grow or maintain their weight, and develop skin disorders and kidney degeneration. The condition can be cured by feeding the unsaturated linoleic or arachidonic acids. It is also demonstrated in dogs. (33) Several clinics have reported that certain eczematous conditions in children are greatly benefited by feeding lard, and may thus be due to deficiency of unsaturated fatty acids. (34)

Fatty acid deficiency has been produced in young, growing animals, or in adult rats first subjected to rather severe starvation. The animals failed to react normally to stress. Experimental wounds failed to heal, and precipitated symptoms of the deficiency condition and death. There was a markedly decreased resistance to X-irradiation. There were no pregnancies in the female deficient mice. (35)

The possibility that high fat intakes are undesirable has been emphasized by studies on the incidence of arteriosclerosis in various countries compared to their usual fat intake. (36) As far as the present data go, countries with low fat intakes also appear to have a low incidence of heart disease and the blood cholesterol levels of the population are lower. The interpretation of such data as cause and effect may well be hazardous since other correlations might also be found. Nevertheless, this indication deserves careful study in view of the large and increasing proportion of fat in the American diet. (36)

Abnormal rumen function due to the excessive ingestion of natural fats may occur under experimental or accidental conditions but it does not occur under normal tent of the ration. The introduction of large amounts of fat into the rumen seems to depress reticulo-ruminal contractions. Partial inhibition of ruminal contractions occurs in sheep as soon as two hours after introducing one-hundred mililiters of emulsified linseed oil into the normal rumen. (37)

Vitamin "A" in Nutrition and Disease

Unless Vitamin "A" or its aldehyde is adequately supplied by the blood the formation of rhodopsin is impaired, giving rise to night blindness or "functional nyctalopia". (38) Apart from the nyctalopia of Vitamin "A" deficiency, most of the other pathological changes follow upon a single cytological change, which affects the mucous membranes throughout the body. These epithelia atrophy and their basal cells proliferate, giving rise to keratinized epithelium comparable with epidermis. The keratinized epithelium is open to bacterial invasion: consequently, severe infections of the eye (xerophthalmia), respiratory organs, genitourinary tract and mouth have been observed in severe Vitamin "A" deficiency. (39)

Wolbach (40) has shown that the primary effect of severe Vitamin "A" deficiency in young animals is complete cessation of endochondral bone growth and the remodeling sequences of normal bone growth. Appositional bone formation continues in conformity with the normal patterns. This arrest in skeletal development occurs prior to the growth failure of soft tissues induced by inanition. The result is overcrowding and pressure on the central nervous system with the formation of multiple herniations of the brain and nerve roots. The myelin sheath degeneration and paralysis resulting from the deficiency in young animals are thus secondary to the bone changes. (41)

Lacrimation and anasarca (edema of the brisket) are the two most common symptoms of a Vitamin "A" deficiency in cattle. (25)

Vitamin "D," Vitamin "A," Calcium, and Phosphorus in Nutrition and Disease

Vitamin "A", Vitamin "D", calcium and phosphorous play an intimate role in

the metabolism of the bones and teeth in domesticated mammals. The following discussion integrates their respective roles in a new concept of the clinical condition traditionally identified as "rickets". This common and nonscientific term, rickets, has been associated with a traditional deficiency of calcium, phosphorus and Vitamin "D" in the growing rat, bird, man and anthrapoid animals in which normal ossification of the cartilage of the bone end does not occur. A clinical condition in domesticated mammals which appeared to be similar to that in the rat, ape and man led to the application of the name and the knowledge of the disease in these species to domesticated mammals. However, it is now becoming apparent that the so-called rachitic condition commonly observed in the calf and pig, and possibly in the lamb, puppy, kitten and foal, involves a lack of Vitmain "A" sufficient to prevent formation of the osteoblasts and osteoid tissue. Vitamin "A" deficiency has not been recognized as a part of the rickets complex in man. Therefore, it seems advisable to identify the condition in domesticated mammals as pseudorickets. Vitamin "D", in addition to Vitamin "A" deficiencies and an improper metabolism or deficiency of calcium and phosphorus are involved in many cases of pseudo-rickets. In severe pseudo-rickets the weight of the body and the tension of the skeletal muscles force the pliable cartilaginous zone of long bones out of shape to cause such things as bowed legs or fractures. Additional signs of pseudo-rickets include arched neck and back, a crouching and painful stance, and poorly developed teeth. The arched neck is probably the earliest indication of rickets in the dog and is a valuable warning of further trouble (42).

Osteomalacia is the disease in adults comparable to rickets in the young. Vitamin D is probably required in appreciable amounts in adults only when the supplies of calcium and/or phosphorus are limiting and the requirements for these minerals are high.

Care must be used in choosing dosage levels of Vitamin D for both treatment and prevention of rickets, since too large a dose can be toxic, producing an abnormally high calcium level in the serum and overcalcification (43). In the most severe cases this can cause widespread calcification of soft tissues, and death. A dosage level can be ascertained only by careful scrutiny of the serum calcium while various levels are tried.

Parturient paresis (milk fever) in the cow is a motor paralysis with a loss of consciousness ordinarily occurring twelve to seventy-two hours after parturition. Clinically, the disease is characterized by tonic muscular spasms and an increased irritability or tetany of the peripheral nerves. Chemically, the disease is characterized by a sudden drop in total blood calcium (hypocalcemia) and especially in calcium concentration. The feeding of moderate to high levels of Vitamin D three to seven days prior to parturition seems to reduce markedly the occurrence of parturient paresis in high producing dairy cows. The Vitamin D either increases calcium absorption or increases mobilization of mineral reserves to meet the needs of parturition.

The Vitamin "B" Complex in Nutrition and Disease

Luecke (43), after reviewing deficiencies of laboratory animals felt that "B" vitamin deficiencies were occuring in farm raised pigs and were perhaps diagnosed as being of infectious origin. In his study, farm raised pigs showing diarrhea, poor thrift, absence of hyperthermia, as well as a history of being fed on a low protein diet were examined carefully to determine the cause of this type of enteritis which would not respond to the recommended therapy prescribed for such conditions, i.e., sulfas and antibiotics. Necropsies of several of these unthrifty individuals showed lesions located chiefly in the large intestine, which were thickened areas, and attached pellets of fecal material and exudate. Edema and areas of congestion could be observed. Degeneration, necrosis, infiltration, and excessive production of mucus were found upon histological examination. Leucocyte counts were slightly above the normal

range of 16,000 to 20,000 cells per cubic millimeter.

To stimulate the poor appetites injections of "B" vitamins were given intraperitoneally. Doses of fifty milligrams thiamine, fifty milligrams riboflavin, two hundred fifty milligrams of niacin and calcium pantothenate each and ten milligrams pyridoxine were used. In addition the animals were placed on a balanced diet and in a matter of thirty to forty days the animals that showed complete recovery exceeded eighty percent in number. Further experimentation showed that niacin and pantothenic acid seem to be those vitamins particularly deficient in the porcine under such conditions.

Ingestion of raw clams with meals reduces the availability of thiamine for man by approximately fifty percent, presumably because of the presence of thiaminase in the clams (44).

The enzyme thiaminase which acts by splitting the thiamine molecule in the digestive tract into thiazole and pyrimidine can be destroyed by thorough cooking of all raw fresh water fish. The cooking now prevents the widespread deficiencies which used to occur in foxes, mink and cats fed raw fresh water fish (carp and herring) (54).

In experimental shock induced in dogs by hemorrhage, the administration of thiamine lowered to normal the elevated keto acid, sugar and lactic acid contents of the blood, and prolonged the survival time and increased the resistance of the animal to shock. (47)

Iron and Copper in Nutrition and Disease

The normal hemoglobin level for newborn pigs is approximately eleven to twelve grams per one-hundred milliliters of blood during the first ten days of life. The level normally decreases to about eight grams per one-hundred milliliters of blood. Thereafter, the hemoglobin level increases gradually until it returns to eleven grams at six months. (48) Suckling pigs frequently develop a simple iron deficiency anemia. The clinical signs of anemia generally occur at about three weeks of age. The pigs may be well developed and apparently well nourished, but they show fatigue, dyspnea, pale skin and blanched, watery mucous membranes. Although the pigs may appear fat and well nourished they will die suddenly and the mortality in some herds is as high as ninety percent from three to four weeks of age. If the suckling pig is limited to its mother's milk as a source of iron the first three weeks, it receives only about one milligram per day (total of twenty-one milligrams). It is sure to develop anemia, since normal rate of growth requires that the pig must absorb and retain three hundred milligrams total for the twenty-one days (49).

Shefby (50), showed in his work at the Virus Research Institute at Cornell University that the use of injectable iron compounds at two days of age greatly increased the pigs' resistance to development of "runts" after being exposed to the transmissable gastroenteritis at ten days of age. His work also revealed high immunity to certain strains of the hog cholera virus among those pigs that had received the injectable iron at two days of age.

The Role of the Vitamins in Antibody Production

Axelrod and Pruzensky designed investigations to study systematically the effects of *specific* individual vitamin deficiencies upon antibody production in the albino rat. They utilized purified diphtheria toxoid as the antigenic stimulus. Serum antibody titer was determined by a hemagglutination reaction involving the use of tannic acid treated sheep erythrocytes coated with the diphtheria toxoid. All efforts were directed toward producing individual deficiencies specific for the vitamin under study. As controls, paired-weighed, paired-fed, and adlibitum fed rats were utilized. All control animals received the same diet as the corresponding deficient group, plus the crystalline vitamin in question.

The failure of simple inanition to modify the antibody response has been demonstrated repeatedly in these studies. Further, no correlation between the inhibiting effect of a vitamin deficiency upon growth rate and upon antibody response

could be shown. Thus, certain deficiencies, e.g., thiamine, caused very marked growth inhibition without greatly affecting antibody response. In other deficiencies, e.g., pteroylglutamic (Folic) acid, a marked decrease in antibody response was noted, although the growth inhibition was relatively slight.

Two further factors might be elucidated. The first is that good antibody responses were observed in many Vitamin A deficient rats. The other factor came to light during the work on anamnestic responses to diphtheria toxoid in pantothenic-acid deficient rats. (Anamnestic reaction, in immunology, is a reaction in which antibodies, which had previously existed and had disappeared from the blood, are redeveloped upon the injection of a nonspecific antigen.) The primary response to the toxoid was obtained three weeks after immunization in the usual manner. As previously noted, this primary response was low in the deficient rats and high in the controls. At this time, a booster shot of the toxoid was given, and the secondary response was determined one week later. In the deficient rats, no secondary response was apparent. Therapy with pantothenic acid during this secondary phase was ineffective in producing a response. Therefore, the mechanisms normally developed in the primary phase that are necessary for the establishment of a booster response fail to materialize when pantothenic acid is lacking. In contrast, the controls show a marked anamnestic response. These data emphasize the need for an adequate intake of pantothenic acid during the primary phase if a booster response is desired. This observation has great clinical practical experience when we think of all the "vaccine breaks" that occur in the field and also consider all the animals that are immunized that must have a deficiency of one of these limiting vitamins. It may also show in part why so many animals fall victim to infectious diseases while exhibiting deficiencies of the well known nutrients.

Parasites in Nutrition and Disease

There are many factors that may contribute to the relationships between the host and the parasite. The food of the host is of extreme importance and is closely linked with the physiologic state of the host. In the intestinal tract, with change in nutrition, there may be a direct effect on the environment of the parasite and thus a possible alteration of the relationship between the host and the parasite. In general, parasites that can establish themselves with the least damage to the host have the best chance for prolonged residence in that host, since, in such cases, the host response to the presence of the parasite is meager or generally ineffectual. The best adjustment of parasite and host is usually found in parasites limited to the alimentary canal. Humans may harbor in their intestinal tract tapeworms such as *Taenia saginata* or flukes such as *Fasciolopsis buske* for many years with no physical effects so long as the diet is sufficient for both the individual and his parasites. Likewise, the intestinal flagellates, as a group, as well as the nonpathogenic amoebae, may persist in the intestine for years without the host being aware of the infection, since these forms are normally harmless commensals. In animal parasitism, the extent of damage produced to the host tissue will vary greatly, and there are many complex factors which must be considered in attempting to explain the pathogenesis of the various forms.

The importance of nutrition in relation to host resistance is a major factor in the pathology of many of the intestinal parasites. Early in 1921, Ackert and his coworkers began a study of the effects of the large round worm of fowls, *Ascaridia galli,* upon its host. These basic studies initiated experimental helminthology in this country. They also uncovered an interesting by-product, as it was shown that there was marked resistance of the chicken to the development of this particular nematode. These investigations led to a much more extensive study of the resistance of chickens to Ascaridia as affected by diets deficient in Vitamins B and A. Ackert and his associates, as a result of these studies, demonstrated for the first time that natural resistance of animals to helminthic infection may be lowered by nutritional deficiencies. In

these experiments, the fowls on the Vitamin A-deficient diets were found to have more and larger worms than did the control chickens. Hiraishi, working concurrently in Japan, fed pigs a diet deficient in Vitamin A and was able to lower their resistance sufficiently to parasitize them with human Ascaris. Payne, Ackert, and Hartman had shown, in swine, that human Ascaris larvae would pass through the somatic phase, but not the intestinal phase, in swine kept on an adequate diet. Clapham, working on the hatching and survival of the horse ascarid, *Parascaris equorum*, in rats, found Vitamin A to be an important factor in resistance. Wright subjected dogs infected with ascarids to diets partially or totally deficient in Vitamin A for periods of 15 to 106 days, and found that the dogs on deficient diets harbored about five times as many worms as did the controls on an adequate diet and exposed to the same degree of worm infection.

The complexity of the problems that are involved in host-parasite relationships vary markedly with the different animal parasites. Rhoads and his co-workers, in 1934, showed that the hypochromic anemias of hookworm disease in Puerto Rico was apparently caused by combination of blood loss, dietary deficiency, and gastrointestinal changes probably resulting from defective nutrition. They found that removal of hookworms, without other therapy, had very little effect upon the anemia or clinical condition of the patient. In contrast to this, they found that with or without removal of the hookworms, the administration of large doses of iron produced rapid improvement of blood values and clinical conditions. This seemed to demonstrate that their was no effect of the hookworms in the intestinal tract of the host other than that due to chronic blood loss. Foster and Cort observed that there was an inverse correlation between anemia and resistance to *Ancylostoma caninum* which could be overcome by periodic bleeding or iron deficiency brought about by a milk diet.

Foster and Cort, by using a diet deficient in Vitamins A and B and minerals, lowered the resistance of dogs previously infected with *Ancylostoma caninum.* After the productivity of the parasites had increased markedly in the dogs on a deficient diet, the hosts were returned to an adequate diet which increased the resistance and caused an extreme inhibition of the egg production of the worms. Foster and Cort showed that as dogs on the deficient diet became more and more emaciated, the development and productivity of the worm parasites increased. The results of this extensive series of experiments furnished further evidence that specific vitamins are important factors in resistance to helminthic infections. These experiments, while not permitting a blanket statement that deficient host diets react to the benefit of the parasite, do indicate that resistance is lowered to helminthic infections, both in the somatic and intestinal phases, when omnivorous hosts are maintained on diets deficient in A, B complex, or D, or on rations with highly restricted sources of protein. These various studies have also shown that the degree of natural and acquired resistance of a host to its helminth parasites is dependent to a large extent upon its diet, its genetic constitution, and its age. Diets of man and other omnivorous animals, to serve in developing the most potent resistance to helminth infections, must include adequate specific vitamins, minerals, and other substances essential to a well balanced ration.

In contrast to the helminths found in the intestinal tract, the single-celled protozoan parasites present a somewhat different problem. A large number of protozoan parasites live in the lumen of the intestinal tract of man and other animals and depend essentially on the diet of the host for their food. Nutritional factors do play an important part, however, in the host parasite relationships in that certain dietary changes may contribute to the decrease of resistance on the part of the host, thus contributing to the production of damage by the parasite.

Protozoologists have long recognized the effect of diet of the host upon the parasite. Hegner (14) in 1924 suggested that a "carnivorous diet", one high in animal protein content, was unfavorable for certain intestinal protozoa of mammals. Hegner and Eskride (15) showed

that rats infected with the human Flagellate, *Trichomonas hominis*, when fed a diet rich in animal protein, produced an unfavorable condition in the cecum of rats for growth and development of this flagellate. Hegner and Eskride (16) also demonstrated that the conditions in the cecum of rats were rendered more favorable for trichomonads when a liver diet was substituted for the normal diet which consisted largely of carbohydrates. Frye and Meleney (17) found that lack of Vitamin A in the diet was not the cause of the inability to establish or maintain infection with *Endamoeba muris* in the rat. Neither the lack of Vitamin A in the diet nor the condition of Vitamin A deficiency in the rats rendered the lumen of the cecum unsuitable for the development of *E. muris*. Ratcliffe showed experimentally that a high protein diet favoring proteolytic bacteria in the intestinal tract decreased the intensity of natural infections with *Endamoeba muris* in mice.

Kagy and Faust, (19) demonstrated that, in dogs, fulminating experimental amoebic colitis could be controlled with raw liver, which at times even produced cure. They demonstrated that liver extract, introduced parenterally, had no effect on the progress of the lesions or symptoms. This is in marked contrast to the results obtained by oral administration of raw liver, which definitely controlled the infection. The authors concluded that the fraction of raw liver that is efficacious as a amoebastatic agent is either different from that which prevents erythropoiesis, or that its amoebastatic action is inhibited when it is introduced intramuscularly. Faust, (21) noted that dogs resistant to infection on a normal diet could usually be infected if they were placed on canned salmon. Kittens fed on salmon diet are also more susceptible to infection with *E. histolytica.*

Sadun (29) showed that guinea pigs fed a combined diet inadequate in ascorbic acid content were highly susceptible to infection with *E. histolytica* even with very small inocula of amoebae.

The experiments showing the relation of dietary factors in various helminth infections is striking. Specific vitamin deficiencies have been shown to favor the parasite and, at the same time, to produce definite interference with host resistance. It has also been established by laboratory experiments that diet is a factor of singular importance in altering the ability of the host to combat certain intestinal helminth infections.

Malnutrition and Resistance To Disease

As many observers have noted, the old concept that famine and pestilence go hand in hand does not always prove true. This was first observed by Underwood (10) in 1789. He stated that at times well nourished children were more susceptible to infection than were poorly nourished ones. Sprunt (11) found that under certain conditions of starvation the rabbit became more resistant to infection with vaccinia. Foster (12) and her colleagues in 1944 indicated a protective effect from a diet low in thiamine or caloric content against the Lansing strain of poliomyelitis virus. Flanigan and Sprunt (8) further substantiated this work in their work on the progressive long term dietary protein depletion on viral susceptibility by using a two host virus system. (1) Swine influenza in the male CF. mouse and (2) Rous Sarcoma virus in New Hampshire red chickens. They were able to show that malnutrition, in itself, is not usually the direct cause of death with the coup de grace being delivered by some terminal infection, that may not have been of significance in a well nourished individual. Their work shows that the effect of host diet on susceptibility to virus infections is not as uncomplicated as was once supposed. A single, deficient diet, constantly administered, has been demonstrated to produce a cyclic susceptibility change.

Autopsy findings lead the authors to these suppositions:

a. First phase of increased susceptibility is the result of the animal consuming his own fat and carbohydrate reserve.
b. Second phase represents a period of increased resistance, which they believe is the metabolic result of using the animals' own protein reserve and thus is running on a "high pro-

tein diet" which increases animals' resistance to infection. (13)

c. The final stage agrees with the corrolary of starvation and pestilence. Basic tissue protein is being utilized which accounts for little resistance.

Tests concerning susceptibility of mice with nutritional disturbances to bacterial infections by Schaldler (14) in 1956, showed that susceptibility increased when animals were placed for five to seven days before infection on a regimen that was deficient, qualitatively or quantitatively, in almost any one of the essential dietary constituents: fats, amino acids, vitamins, etc.

The susceptibility of mice to the Poliomyelitis virus is decreased by restricting the thiamine intake, and this effect has been shown to be specific for thiamine and not due to the inanition of deficient mice. (46)

EXPERIMENTAL PRODUCTION OF Pneumonia in Lambs. Forty-one lambs were exposed to a virus, pleuropneumonia-like organisms, and Pasteurella organisms recovered from pneumonic lesions of lambs. None were capable of reproducing pneumonia when used singly.

Pneumonia was not produced by stress when applied alone.

A combination of any two of the three infectious agents resulted in a febrile response in five of seven lambs but no pneumonic lesions.

Combinations of the three microbial agents produced pneumonic lesions in two of four lambs.

When stress was applied with a combination of two or three agents, all of seven lambs developed both clinical signs and lesions of pneumonia.

(Handy, A. H., and Pounden, W. D. Experimental Production of Pneumonia in Lambs, Am. J. Vet. Res. 20:78–83, 1959).